

REMARKS

1. Applicant's Record of the substance of Interview

Examiner Nichols and Supervisory Patent Examiner Kunz are thanked for according Counsel a telephonic interview on March 10, 2004. In supplementation of the interview summary record, we make the following remarks. No prior art was discussed. The proposed amendments discussed were those set forth in the draft main claims for discussion purposes faxed March 4, 2004. The Examiner said that the claims could not be broadened to include SEQ ID NOs other than 1-4, 9, 12, 14, 15, 17 and 19-22 as that would require additional searching. Likewise, since the case was "after final", they did not want to analyze the basis for multimers other than those explicitly depicted/described in the specification and drawings. Agreement was reached that Applicants were entitled, not only to SEQ ID NOs:1-4, 9, 12, 14, 15, 17 and 19-22 (as conceded on page 4 of the office action) but also to "dendrimers" in which four of these peptides are covalently linked to a lysine backbone to form a covalent conjugate.

Agreement was also reached that Applicants were entitled to a method of using the aforementioned compounds to stimulate or promote neurite outgrowth, or proliferation of, NCAM presenting cells.

Applicants reserve the right to pursue broader claims in a continuation application.

2. Restriction/Election (OA §§5-6)

2.1. Method claims 114, 119-121, and 129-131 are now dependent, directly or indirectly, on claim 98. If claim 98 is deemed allowable, then they should be rejoined pursuant to MPEP 821.04.

2.2. Prosthetic nerve guide claim 131 is related to claim 98 as combination to subcombination. If the subcombination is

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patentable, 131 should be rejoined.

3. Specification (OA §7)

The objection to the specification is not understood. First, what is meant by "the Amendment filed 15 September 2003 does not incorporate any changes to the Specification as filed"? That amendment appears to amend pages 23, 24, 45, 47, 48, 58, 61, and 62.

Secondly, if the problem is that the amendment of 15 September 2003 is not in proper form, and hence was not entered, then what is the position of the PTO as to the supplemental amendment filed September 16, which address the same pages? Was it entered? Does it resolve the April 15 objections?

Finally, if it does not resolve those objections, how, specifically, is it defective? What exactly should Applicants do to lay this issue to rest?

4. Sequence Rule Objection (OA §13)

4.1. Applicants hereby submit (1) the paper copy of a "Sequence Listing", complying with §1.821(c), to be incorporated into the specification as directed above, and (2) the Sequence Listing in computer readable form, complying with §1.821(e) and §1.824, including, if an amendment to the paper copy is submitted, all previously submitted data with the amendment incorporated therein.

4.2. The undersigned attorney or agent hereby states as follows:

- (a) this submission does not include new matter [§1.821(g)];
- (b) the contents of the paper copy (as amended, if applicable) and the computer readable form of the Sequence Listing, are the same [§1.821(f) and §1.825(b)];
- (c) if the paper copy has been amended, the amendment is supported by the specification and does not include new matter [§1.825(a)]; and

- (d) if the computer readable form submitted herewith is a substitute for a form found upon receipt by the PTO to be damaged or unreadable, that the substitute data is identical to that originally filed [§1.825(d)].

4.3. Under U.S. rules, each sequence must be classified in <213> as an "Artificial Sequence", a sequence of "Unknown" origin, or a sequence originating in a particular organism, identified by its scientific name.

Neither the rules nor the MPEP clarify the nature of the relationship which must exist between a listed sequence and an organism for that organism to be identified as the origin of the sequence under <213>.

Hence, counsel may choose to identify a listed sequence as associated with a particular organism even though that sequence does not occur in nature by itself in that organism (it may be, e.g., an epitopic fragment of a naturally occurring protein, or a cDNA of a naturally occurring mRNA, or even a substitution mutant of a naturally occurring sequence). Hence, the identification of an organism in <213> should not be construed as an admission that the sequence *per se* occurs in nature in said organism.

Similarly, designation of a sequence as "artificial" should not be construed as a representation that the sequence has no association with any organism. For example, a primer or probe may be designated as "artificial" even though it is necessarily complementary to some target sequence, which may occur in nature. Or an "artificial" sequence may be a substitution mutant of a natural sequence, or a chimera of two or more natural sequences, or a cDNA (i.e., intron-free sequence) corresponding to an intron-containing gene, or otherwise a fragment of a natural sequence.

The Examiner should be able to judge the relationship of the enumerated sequences to natural sequences by giving full consideration to the specification, the art cited therein, any

further art cited in an IDS, and the results of his or her sequence search against a database containing known natural sequences.

5. Enablement Rejection (OA §14-28)

The Examiner conceded enablement for the polypeptides of SEQ ID NOS:1-4, 9, 12, 14, 15, 17 and 19-22, but not for a mimic of an NCAM fragment which comprises the sequence



In Example 3, Applicants disclosed the synthesis and screening of what is called a "decapeptide library". The peptides were actually 11-mers; the library design was A-X<sub>10</sub> where X is any amino acid other than Cys or His. Thus, by "decapeptide library", applicants meant a library of 11-mers with 10 variable amino acids. This is apparent from Fig. 4A.

The library was screened with the receptor NCAM Ig1-PP, i.e., the isolated Ig1 domain of NCAM.

As stated in Example 4, Fig. 4A shows the sequences of the 22 peptides from "the most intensely stained beads", i.e., the peptides which most strongly bound NCAM Ig1-PP.

We wish to note that the sequences in question are not fragments of NCAM, as assumed by the Examiner. The NCAM fragments are IG1-P (ID 26) and IG2-P (ID 23). See P61, L13-17.

Since SEQ ID NOS: 1-4, 9, 12, 14, 15, 17 and 19-22 were identified on the basis of their ability to bind the isolated Ig1 domain of NCAM, but only SEQ ID NOS:1-3 have been tested for activity against NCAM presenting cells, (P64, L10-13; Fig. 7) we have excised the cellular activity limitation from claim 98 and moved it into new claim 149. The method claims recite a cellular effect, and hence are dependent on 149.

It appears to us that applicants are entitled to a broader definition of the functional motif (a peptide comprising at least

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two basic amino acid residues) which was taught at P23, L29-32. This definition would embrace SEQ ID NOs:1-12, 14-23, 27, 28 and 32-37. However, we have been advised by the examiners that in view of the "after final" status of the case, we cannot shift to this broader definition at this time.

We turn next to the issue of dendrimers. Original claims 45 and 46 read as follows:

45. The pharmaceutical composition according to any of the claims 42-44, wherein the compounds are formulated as multimers.

46. The pharmaceutical composition according to any of the claims 42-44, characterised in that the compounds are formulated as dendrimers, such as four peptides linked to a lysine backbone, or coupled to a protein carrier such as BSA.

Also P49, L13-19 discloses

In a preferred embodiment, the peptides are formulated as multimers, e.g. bound to carriers. The peptides may suitably be formulated as dendrimers such as four peptides linked to a lysine backbone, or coupled to a polymer carrier, for example a protein carrier, such as BSA.

See also P44, L13-15. Dendrimers are actually depicted in Fig. 2, and P63, L14-16 refers to synthesis of dendrimers consisting of "four peptide-monomers coupled to a backbone consisting of three lysines".

There is ample experimental evidence of the activity of multimers. The Examiner's attention is first directed to P61, L29-34, disclosing preparation of dendrimers of peptides C3 (ID1), D3 (ID2) and D4 (ID3):

Synthesis of peptide dendrimers was accomplished by coupling Fmoc-Lys(Fmoc)-OH (Novabiochem) to the linker resin followed by Fmoc-deprotection of the Fmoc group and further coupling of Fmoc-Lys (Fmoc)-OH was

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performed. After Fmoc-deprotection the synthesis of peptides was performed as above for the monomeric peptides.

Example 6 showed that these dendrimers bind to the NCAM Ig1 domain, see P63, L14-27). Example 7 reports additional activity of these dendrimers, see P64, L14-21. At P64, L34 to P65, L3, the specification states:

Different forms of the C3 peptide were tested. It was found that monomeric, dendrimeric and BSA-coupled forms of C3 had similar effects on aggregation. However, the dendrimer of the C3 sequence was the most potent form, presumably due to the ability to link several of the receptor domains.

We also prepared a dendrimer derivative (Ig2-Pd) of the of the Ig2 peptide (Ig2-P, ID23) and found it to be active (P70, L24-35).

Finally, there is the active dendrimer disclosed in Fig. 7, wherein the monomer is ID32.

The Examiners were not certain that the term "dendrimer" is properly applied to a covalent conjugate. While Counsel disagrees, all recognized that the issue could be avoided simply by eschewing the word "dendrimer" in characterizing the compound.

The Examiner, in the interview summary record, says that the backbone is "tetrалysine". However the disclosure at P63, L14-16 refers to use of three lysines.

A lysine backbone of only three lysines is sufficient to couple together four peptide moieties. Each lysine has, in effect, three valences, the NH<sub>2</sub> and COOH groups attached to the alpha carbon, and the epsilon amino group. Thus, Lys1 could be attached through its alpha and epsilon amino groups to the COOH groups (forming a peptide bond) of Lys2 and Lys3, and each of these could hold two peptide moieties through like

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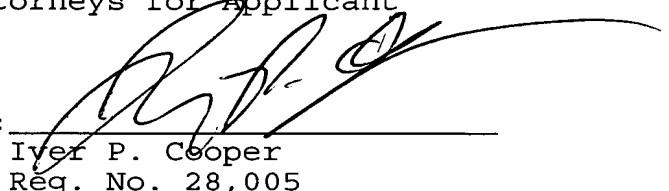
attachments to their amino functions.

Alternatively, Lys1 could bear one peptide, and be covalently linked to Lys2, Lys2 could bear one peptide and be covalently linked to Lys3, and Lys3 could bear two peptides.

Respectfully submitted,

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Enclosure

-Sequence Listing (Paper Copy and CRF)

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